Effect of migration and environmental heterogeneity on the maintenance of quantitative variation: a simulation study

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Running Title: *Environmental heterogeneity and maintenance of variation*

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Keywords: *mutation-selection balance, theory, genetic variation, migration, environmental heterogeneity*

1   Abstract

2   The paradox of high genetic variation observed in traits under stabilizing selection is a

3   longstanding problem in evolutionary theory, as mutation rates are 10-100 times too low to

4   explain observed levels of standing genetic variation under classic models of mutation-selection

5   balance. Here, we use individual-based simulations to explore the effect of various types of

6   environmental heterogeneity on the maintenance of genetic variation (V_A) for a quantitative trait

7   under stabilizing selection. We find that V_A is maximized at intermediate migration rates in

8   spatially heterogeneous environments, and that the observed patterns are robust to changes in

9   population size. Spatial environmental heterogeneity increased variation by as much as 10-fold

10   over mutation-selection-balance alone, whereas pure temporal environmental heterogeneity

11   increased variance by only 45% at max. Our results show that some combinations of spatial

12   heterogeneity and migration can maintain considerably more variation than mutation-selection

13   balance, potentially reconciling the discrepancy between theoretical predictions and empirical

14   observations. However, given the narrow regions of parameter space required for this effect, this

15   is unlikely to provide a general explanation for the maintenance of variation. Nonetheless, our

16   results suggest that habitat fragmentation may affect the maintenance of V_A and thereby reduce

17   the adaptive capacity of populations.

18   Introduction

19   As genetic variation is the fundamental basis upon which evolution acts, it is important to

20   understand how variation is maintained in order to provide a foundation for answering various

21   questions in biology and related fields, such as missing heritability (Maher, 2008), conservation

22   of biodiversity (Cook & Sgrò, 2017), and population potential to respond to change (Houle,

23   1992). And yet, the relative importance of factors that influence variation and the mechanism(s)

24   under which it is maintained are not wholly understood (Barton & Turelli, 1989; Mackay *et al.*,

25   2009). The majority of quantitative traits experience stabilizing selection, which in theory should

26   erode genetic variation. However, high levels of standing variation and heritability of

27   quantitative traits are consistently observed in nature (Johnson & Barton, 2005). This paradox – a

28   high degree of genetic variation maintained in the face of stabilizing selection – remains a

29   longstanding, unsolved problem in evolutionary biology and quantitative genetics theory.

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31   The most widely studied explanation for this paradox is mutation-selection balance (henceforth

32   referred to as MSB), the appeal of which lies in its intuitive logic: mutation, as the ultimate

33   source of genetic variation, provides enough input to offset the eroding effect of selection,

34   leading to a state of equilibrium. Under such models, stabilizing selection is assumed according

35   to a Gaussian fitness function with parameter V_S setting the strength of selection on genotypes

36   (where large values result in weaker selection). Multiple MSB models have been proposed, most

37   notably the continuum-of-alleles model from Kimura and Crow (1964) of which two main

38   approximations have been put forth: the Gaussian approximation (Kimura 1965; later expanded

39   by Lande 1976), and the House-of-cards approximation (Turelli, 1984; Bu☐rger *et al.*, 1989).

40   The continuum-of-alleles model makes the basic assumption that for a locus with a continuous

41   distribution of possible alleles, mutation can result in a new allele with an effect different from

42   the pre-existing one. In general, the two approximations differ in the way each handles this

43   assumption. For example, for an arbitrary diploid locus i with an allele of effect x_i and a mutation

44   with effect y_i, under the Gaussian approximation the mutated allele would take on a new value

45   which is conditional on the previous state $(x_i + y_i)$. This results in a predicted equilibrium genetic

46   variance $V_G(G) \cong 2n\sqrt{\mu\alpha^2 V_S}$, where n is the total number of loci that compose the quantitative

47   trait, μ the per locus mutation rate, and α^2 the variance of the distribution of mutational effects.

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48   Under the House-of-Cards approximation, x_i may take on any effect independent from $x_{i+1}…x_n$,

49   and mutation results in the replacement of x_i by y_i. In this case, the predicted equilibrium

50   variance, $V_G (HC) \cong 4n\mu V_S$ is independent of the distribution of mutation effects. In contrast with

51   the continuum-of-alleles model, there is the diallelic model (Bulmer, 1972; Barton, 1986), which

52   assumes only two possible values at a locus with equal forward and backward mutation rates,

53   such that mutation causes a flip between states (*e.g.*, $xi = \{0,1\}$). In this case, the resulting

54   equilibrium variance has been shown to be generally comparable to $V_G(HC)$.

55   Although these models have been extensively studied, conflicting evidence over their

56   applicability in relation to realistic biologic parameters has left debate open (Barton & Turelli,

57   1989; Johnson & Barton, 2005; Zhang & Hill, 2005). The assumptions and requirements of these

58   models are unrealistic: primarily, they require extreme mutation rates or too many loci per trait

59   (Johnson & Barton, 2005). This can be most simply illustrated by considering two empirical

60   observations: heritability, h^2, for the majority of traits are relatively high ($h^2 = 0.2 \sim 0.6$;

61   Mousseau and Roff 1987), and stabilizing selection is typically relatively strong in nature, as

62   evidenced by the median value of estimates of reported quadratic selection gradient ($\gamma = -0.1$;

63   (Kingsolver *et al.*, 2001). The value $\gamma = -0.1$ implies that the ratio of selection to phenotypic

64   variation is $V_S / V_P = 5$ (Kingsolver *et al.*, 2001; Johnson & Barton, 2005), which can be

65   rearranged to account for typical estimates of heritability, yielding an expected empirical range of

66   values for variation maintained in a natural population of approximately $0.04 < V_A / V_S < 0.12$.

67   Putting this in the context of Turelli's (1984) $V_G(HC)$ model under the assumption that $V_G \sim V_A$,

68   then $0.01 < n\mu < 0.03$. If there are 100 loci underlying a given trait, then this would require per-

69   locus mutation rates on the order of $\sim 10^{-4}$, which is 10 to 100 times higher than most estimates

70   from quantitative genetic studies, typically thought to be in the range of 10^{-6} to 10^{-5} (Barton &

71   Turelli, 1989; Bu☐rger, 2000).

72   More complex extensions of these models have been investigated (Bu☐rger *et al.*, 1989; Zhang

73   & Hill, 2002; Zhang *et al.*, 2002, 2004), namely by extending to multiple traits, such that

74   'apparent stabilizing selection' is generated through pleiotropic effects. Pure pleiotropy and joint

75   effects models have been studied, as well as other extensions to include factors such as

76   dominance or balancing selection. Nonetheless, these models have yet to provide a sufficient

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77   explanation for the patterns of variation maintained as suggested by empirical data (Johnson &

78   Barton, 2005; but see Zhang and Hill 2005).

79   The above models all assume stabilizing selection to a constant environment, and yet

80   environments varying in space and time can also affect the maintenance of variation. If

81   environmental heterogeneity can maintain sufficient differences in allele frequencies within a

82   subdivided population, and migrant individuals introduce novel variants that can be maintained

83   for some time, then migration can result in an increase in genetic variation within a population.

84   Structured populations with limited amounts of gene flow have the potential to increase within-

85   population variance (Lythgoe, 1997; Tufto, 2000; Spichtig & Kawecki, 2004), and a temporally

86   fluctuating environment has been shown in some cases to increase variance under particular

87   regions of parameter space (Kondrashov & Yampolsky, 1996; Bürger & Gimelfarb, 2002;

88   Gulisija & Kim, 2015). However, these studies have not explicitly framed results in terms of the

89   relative increase in variance over mutation-selection to address the problem of the discrepancy

90   between MSB predictions and empirical observations, and the effect(s) of time and space have

91   not been investigated simultaneously.

92   Here, we assess how different kinds of environmental heterogeneity affect the maintenance of

93   genetic variation. We simulate spatial and temporal heterogeneity both independently and

94   simultaneously to explore how the maintenance of variation is affected by variation in migration

95   rate, population size, mutation rate, strength of selection, and pattern of environmental variability.

96   In all cases, we explicitly focus on comparing heterogeneous vs. homogeneous environments to

97   represent the increase in variance relative to that expected under mutation-selection balance. This

98   provides some indication of how much more variance can be maintained under heterogeneous

99   environments, which can be compared to the discrepancy between the mutation-selection balance

100   predictions and empirical observations described above.

Methods

Simulation Setup

103   A diploid Wright-Fisher two-population scenario was modeled using the stochastic, individual-

104   based simulation program *Nemo* (*v2.3.45*; Guillaume and Rougemont 2006) under various

105   parameter combinations of population size N (1000, 10000), strength of selection V_S (2, 5, 10),

106   mutation rate μ (10^{-6}, 10^{-5}, 10^{-4}), and backwards migration m (rate ranging from 10^{-5} to 0.1 per

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107   generation) between two equal sized patches with some local optima θ. See Table 1 for detailed

108   reference of all parameters.

109   In each simulation, relative fitness is determined by Gaussian stabilizing selection acting on a

110   single quantitative trait of 50 unlinked loci, each with an independent allelic value a ($n = 50$; $r =$

111   0.5). Nemo defines individual fitness of a quantitative trait according to the equation:

$$W(z) = exp\left[-\frac{(z - \theta)^2}{2w^2}\right]$$

112   Where z is the phenotypic value of the individual, equal to Σa_i, θ the local optimum, and w^2 the

113   strength of selection on the phenotype ($V_S = w^2 + V_E$). As no effect of environmental variance

114   was included ($V_E = 0$), hereafter we use V_S to represent the strength of selection on the genotype

115   to simplify comparison to theoretical models. The allelic value (a) at each locus is randomly

116   drawn from a gamma distribution (mean = 0.05, shape = 1), with mutation causing a change of

117   states $\pm a$ (this follows a pseudo-diallelic model with a House-of-Cards mutation scheme). Loci

118   have additive effects on the phenotype, with no dominance or epistasis and free recombination

119   between adjacent loci ($r = 0.5$). Thus, genetic architecture cannot evolve through addition of

120   multiple successive mutations at a given locus or through competition among alleles with

121   different linkage relationships.

122   A total of six scenarios were run, each differing in the relation of local optima between patches:

123   (1) **Homogenous patches** ($\theta_1 = \theta_2 = 1$). The control set used for comparison to the other

124   scenarios; the local optimum is the same in each patch such that any differences that arise are

125   due to drift rather than selection.

126   (2) **Pure spatial heterogeneity** ($\theta_1 = +1$; $\theta_2 = -1$). This set of simulations introduced spatial

127   environmental heterogeneity with opposite local optima between each patch.

128   (3) **Pure temporal heterogeneity** ($\theta_{t,1} = \theta_{t,2}$). To reflect a population inhabiting a changing

129   environment, temporal fluctuations were modelled using an oscillating optimum defined by a

130   sine wave centered about zero with amplitude of 1; $\theta(t) = \sin\left(\frac{2\pi t}{P}\right)$. Simulations were run

131   with varying periodicity (P = 4, 16, 40, 100, 1000). The main focus of the analysis considers a

132   temporal oscillation over 100 generations, unless otherwise specified.

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133   (4) **Combined (Spatial & Temporal) heterogeneity.** The last set of simulations combined the

134   setup of (2) and (3). Three subsets were used to represent differing degrees of spatial

135   variation (see *SI*): (*A*, $\theta_{t,1} = -\theta_{t,2}$) opposing optima reflected about the horizontal axis; (*B*, $\theta_{t,1}$

136        $= \theta_{t,2} + 2$) in phase temporal fluctuations with one patch oscillating about -1 and the other

137   about +1; (*C*, $\theta_{t,1} = \theta_{t+(P/4),2}$) a partial phase shift between optima functions, such that θ_2 lags

138   behind θ_1.

139   All simulations were run for an initial period of 40,000 generations under these conditions,

140   allowing the trait value to stabilize at an approximate equilibrium (assessed visually for the

141   absence of change in trajectory of the trait value over time). A census of the population was taken

142   every *t* generations (t=100, or t=5 for temporal simulations with $P \leq 100$ generations) for the

143   mean trait value and genetic variation (in terms of V_A, the additive genetic variation) present in

144   each patch. This data was averaged over the stable period of the last 10,000 generations (1000 for

145   temporal simulations with $P \leq 100$) for 40 replicates. For consistency, a 40x50 matrix of allele

146   values was generated such that each replicate had a different complement of mutation effect

147   sizes, but that this complement was held constant across all simulation scenarios. Under the

148   simulations that included temporal heterogeneity, preliminary results showed a cycling pattern

149   emerge for both the trait value and V_A over time; to use an estimate as representative as possible,

150   the V_A maintained within a cycle was sampled at 20 evenly spaced time-points within a cycle,

151   and the mean calculated over the last ten cycles of the simulation. To obtain a measure of

152   variation maintained within the simulated population that is comparable to empirical evidence,

153   the ratio V_A / V_S was calculated from the final mean V_A estimate of each simulation set. All data

154   processing and analysis was done with R v3.3 (R Development Core Team, 2016).

Results

156   **Pure Spatial Homogeneity, Set 1 ($\theta_1 = \theta_2 = 1$)**

157   We first describe patterns in the homogeneous environment, which acts as a control

158   demonstrating the effect of finite population MSB processes in a two-patch model, to study the

159   effects of mutation rate (μ), selection strength (V_S), and population size (N), on the maintenance

160   of variation (Figure 1A). As expected from quantitative genetic theory (Falconer and Mackay

161   1996), variance was somewhat higher in larger populations, although the difference is minimal

162   under most parameters (Figure S1). Also following expectations, V_A increases with μ, with the

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163   effect of mutation rate approximately linear, and independent of selection. Similarly, V_A

164   increases with V_S (selection weakens), which qualitatively matches predictions of Turelli (1984),

165   Burger et al. (1989), and as observed by Yeaman and Guillaume (2009), although some

166   deviations occur due to differences in the mutation model. While from Figure 1 there appears to

167   be an interaction between selection and mutation rate, the relative effect of a ten-fold increase in

168   mutation (from $\mu = 10^{-5}$ to $\mu = 10^{-4}$) is similar for $V_S = 2$ versus $V_S = 10$ (V_A changes by a factor

169   of 8.87 vs 8.59 for $V_S = 2$ vs $V_S = 10$; $m = 0.1$).

170   Notably, these patterns are qualitatively independent of N (Figure S1), and so the results below

171   are presented for the subset of N = 1000 only. There is minimal response to rate of migration

172   between the two patches, except for a small increase at low to intermediate m, which is consistent

173   with predictions of Goldstein and Holsinger (1992), and arises due to an interaction between

174   effects of genetic redundancy and genetic drift (hereafter, referred to as the "redundancy-drift

175   effect"; see Discussion).

176   **Pure Spatial Heterogeneity, Set 2 ($\theta_1 = +1$; $\theta_2 = -1$)**
177   With spatial environmental heterogeneity, two key differences arise when compared to the

178   control case (Set 1): an overall large increase in the amount of V_A maintained, and the appearance

179   of a threshold at high migration, above which the divergence among populations and amount of

180   V_A maintained both decrease (which is qualitatively consistent with the critical migration

181   threshold predicted by Yeaman and Otto, 2011). While the migration rate at which V_A peaks

182   varies as a function of V_S, the maximum V_A reached under these parameters ($\cong 0.32$) is similar

183   among levels of V_S. Given the number of loci, mutation effect sizes, and mutation rates that we

184   used, spatial environmental heterogeneity generates up to a ~10-fold increase in V_A compared to

185   the homogenous case (for the same parameters, V_A[homogeneous] = 0.033), as shown in Figure

186   1B. This demonstrates that the redundancy-drift effect described previously by Goldstein and

187   Holsinger (1992) is small relative to the effect of migration and spatial heterogeneity, at least

188   under these conditions. Additionally, the effect of mutation becomes relatively less pronounced

189   under spatial heterogeneity, as most of the variation is maintained by migration in this case.

190   Whereas a ten-fold change in μ (from $\mu = 10^{-5}$ to $\mu = 10^{-4}$) results in an increase by a factor of

191   8.87 in Figure 1A, this increase only changes V_A by a factor of 1.09 under spatial heterogeneity

192   ($V_S = 2$, $m = 0.1$).

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193 **Pure Temporal heterogeneity, Set 3 ($\theta_{t,1} = \theta_{t,2}$)**

194 In contrast to the case with spatial heterogeneity, under a temporally fluctuating optimum there is

195 in general little change in V_A in comparison to Set 1, the homogenous case. As shown in Figure

196 2A, a similar qualitative pattern is observed in response to migration rate, with an increase at low

197 to intermediate m and rapid drop with $m > 0.001$, akin to the redundancy-drift effect observed in

198 the homogeneous case. The resulting maximum peak in V_A however is approximately 45%

199 greater than the homogeneous case ($V_S = 5$, $\mu = 10^{-4}$, $m = 2.5 \times 10^{-4}$), suggesting that temporal

200 heterogeneity can only marginally increase the importance of this effect.

201 Multiple lengths for the temporal oscillation of the environment (denoted as P) were simulated to

202 test the influence of the period length on the qualitative patterns observed, and complex

203 interactions were found (Figure S2.1). Setting P $\leq$ 100 resulted in a response to migration similar

204 to the homogeneous case and an overall increase in V_A with μ, as expected. However, the

205 behavior for P = 100 deviates under very strong selection ($V_S = 2$), with the redundancy-drift

206 effect causing a peak in V_A at lower migration rates than for shorter periodicities (see Figure 2A

207 and S2.1). Across changes in all parameter combinations, the redundancy-drift effect causes a

208 maximum increase in V_A of 28% relative to the V_A maintained under $m = 0.1$, which was

209 observed for P = 100 and $V_S = 10$. Under a very long cycle (P = 1000 generations), there is

210 minimal response to migration rate (i.e., no effect of redundancy-drift) and very little increase in

211 variance when $\mu = 10^{-6}$ relative to simulations with shorter periods, but much more increase in

212 variance under long periods at $\mu = 10^{-4}$ (see Figure S2.1; V_A under P = 1000 is 1.3 ~ 2.5-fold

213 higher than P = 100 under $\mu = 10^{-4}$). The degree of increase in V_A under temporal heterogeneity

214 relative to homogeneity therefore depends on mutation, period, and selection, but is typically

215 considerably less than under spatial heterogeneity with intermediate migration.

216 **Combination of Spatial and Temporal heterogeneity, Set 4**

217 For spatial and temporal heterogeneity combined ($\theta_{t,1} = \theta_{t,2} + 2$; see *SI* for illustration), the

218 amount of V_A and patterns that arise are qualitatively similar to those in the case of pure spatial

219 heterogeneity. Similar threshold behavior is observed, and similar levels of V_A are maintained,

220 peaking between migration rates of 0.01 ~ 0.1, again depending on V_S (Figure 2B). Under this

221 form of combined spatial and temporal heterogeneity, there is a max 31% increase in V_A

222 compared to pure spatial heterogeneity (at $V_S = 5$, $\mu = 10^{-4}$, $m = 0.001$), which is very small when

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223   compared to the 9.75-fold difference in V_A for the pure spatial heterogeneity vs. homogeneity

224   under the same parameters V_S and μ.

225   In contrast, the complex patterns involving periodicity described above that were observed in the

226   purely temporal set do not appear to carry over under combined spatial and temporal

227   heterogeneity, likely because they are swamped out by the relatively larger effect of migration,

228   which is relatively consistent across different period lengths (see S2.2). There is an overall

229   increase in V_A maintained, which appears more similar to the case of pure spatial heterogeneity

230   than pure temporal heterogeneity or homogeneity. This result is perhaps unexpected, as spatial

231   and temporal effects of heterogeneity might be expected to work synergistically.

Comparing Sets

233   Figure 3 shows a comparison amongst the six different patterns of environmental variation for a

234   subset of the total parameter combinations used. For a given parameter set, there is a general

235   trend of increased V_A maintained with an increase in heterogeneity, particularly with the degree

236   of spatial heterogeneity between patches. Temporal heterogeneity on its own does little to

237   increase V_A compared to the homogeneous set. When temporal heterogeneity is combined with

238   spatial heterogeneity, the increase in V_A is most pronounced in sets where the temporal

239   fluctuations in the two patches are most out of phase (Figure 3; see *SI* for relation between $\theta_{t,1}$ and

240     $\theta_{t,2}$). Of the three combinations investigated, subset 4B – where $\theta_{t,1} \neq \theta_{t,2}$ for any t – maintains a

241   considerable higher level of V_A compared to subset 4A, which in turn maintained more V_A than

242   in 4C, which was most in phase between patches. This further supports the emphasis on spatial

243   heterogeneity over temporal heterogeneity as a stronger force for maintaining variation.

244   To explore whether environmental heterogeneity could yield more realistic ratios of V_A / V_S (ie,

245     $0.04 < V_A / V_S < 0.12$), we compared values for this ratio under homogeneous vs. heterogeneous

246   simulation scenarios with all other parameters held constant (Figure 4). Without any spatial

247   heterogeneity, none of the parameter combinations result in V_A that falls within this range for

248   expected typical values (see S4, S5 for simulation sets that did not fall into range). However, with

249   spatial heterogeneity, the combination of high migration ($m \geq 0.01$) and strong selection ($V_S = 2$

250   or 5) does result in V_A within the typical range (i.e. an increase of ~10x relative to MSB). For the

251   combination of spatial and temporal heterogeneity, there is little change for most parameter

252   combinations compared to spatial heterogeneity alone (Figure 4B); for those where there is a

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253   noticeable deviation, whether the parameter set falls in or out of the target range remains

254   unchanged (with an exception at $V_S = 2$, $m = 0.001$).

Discussion

256   The results of these simulations show that environmental heterogeneity can have a large impact

257   on the maintenance of additive genetic variation (V_A) under a variety of parameters. The

258   direction and magnitude of this impact depends upon the rate of migration between

259   subpopulations, with intermediate rates of dispersal providing the largest effect. This effect is

260   also dependent on the type of environmental heterogeneity – spatial, temporal, or a combination

261   of both all result in different magnitude and pattern of response to migration. Spatial

262   heterogeneity has a much larger effect than temporal, and the effect of combined heterogeneity

263   increases with the degree of spatial difference when temporal oscillations in each patch are more

264   out of phase.

The Redundancy-Drift Effect

266   For a range of migration rates (dependent on V_S and μ) spatial environmental heterogeneity

267   substantially increases the variation a population can maintain. However, migration alone, even

268   between two environmentally similar patches, can increase the variation maintained at very low

269   rates of migration. This result is due to the interaction of genetic redundancy and the stochastic

270   force of genetic drift, as described by Goldstein and Holsinger (1992). With enough population

271   structure (i.e., limited gene flow), the genotypes existing in each patch are expected to undergo

272   different histories of mutation and drift, resulting in relatively independent fluctuations in allele

273   frequency within each patch, and possibly local fixation or loss. Over time, this results in a

274   different pool of genotypes present in each patch, even if the mean phenotype is equivalent.

275   Migration between patches with different allele frequencies will then increase the variance within

276   patches; movement of individuals adapted to a given environment with one complement of

277   alleles that result in a similarly fit phenotype, such that it can be maintained in the new

278   population, then this flux of allelic variants/combinations should increase the variation

279   maintained in the population. This effect is mainly dependent on two factors: (1) the number of

280   possible redundant genotypes, and (2) the degree of population structure – patches must be

281   sufficiently connected such that new genotypes can be introduced by migration at a high enough

282   rate to affect genetic variance, but not overly connected such that drift is no longer acting

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283   (relatively) independently in each patch. This genetic redundancy-drift effect is evident in the

284   control case, where there is an observable – albeit minimal – response to low migration, which

285   persists regardless of population size, rate of mutation, or strength of selection. This effect is

286   somewhat increased under temporal heterogeneity, resulting in larger peaks over the same range

287   of low dispersal as the homogeneous case, particularly under high mutation and strong selection

288   ($\mu = 0.0001$, $V_S = 2$). The increase of this effect may be due to the temporally variable selection

289   within each patch causing different alleles to change in frequency more rapidly than migration

290   homogenizes differences, resulting in a larger pool of differentiated loci than would be generated

291   by drift alone.

Environmental Heterogeneity

293   Nonetheless, this redundancy-drift effect is small relative to the effect of spatial heterogeneity. In

294   this case, selection acts to pull each subpopulation towards its optima, resulting in different allele

295   frequencies within in each patch. With migration, the alleles that would otherwise be purged by

296   selection are persistently reintroduced into the other patch, increasing the V_A maintained in the

297   population. However, there is a threshold behavior to this system – a critical migration rate

298   beyond which polymorphism can no longer be maintained (Felsenstein 1976; Yeaman and Otto

299   2001). Past this point, the allele frequencies of each patch are similar enough that migrants are

300   much less likely to re-introduce novel/differentiated alleles, and the effect of migration on V_A is

301   reduced.

303   Most populations experience some form of temporally variable selection, be it seasonal

304   fluctuations or some otherwise unstable environment. Due to this, there has been much interest

305   around fluctuating selection and its effect(s) on the maintenance of variation (Kondrashov &

306   Yampolsky, 1996; Bürger & Gimelfarb, 2002; Siepielski *et al.*, 2009; Morrissey & Hadfield,

307   2012; Gulisija & Kim, 2015). Difficulties arise when attempting to draw comparisons across such

308   studies due to a variety of different assumptions, such as the way in which the moving optimum

309   is modelled and the nature of the underlying genetic architecture. A simple sinusoidal wave is

310   generally used, but varying parameters of this function (amplitude, center, periodicity) appear to

311   have complex interactions with each other as well as other parameters such as mutation rate and

312   genetic redundancy.

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313 Burger and Gimelfarb (2002) found that in a diallelic multi-locus model with recurrent mutation,

314 the relative genetic variance increased with period length (typically $\geq$ 24 generations), but the

315 magnitude of change and pattern of response to period depended on the amplitude of the

316 oscillations. They observed the highest levels of genetic variance when the amplitude was set

317 such that the optimum cycled between the most extreme possible genotypes, and that greater

318 amplitudes, where the optimum fell beyond the maximum possible genotypic values, resulted in a

319 decline in V_A at high period lengths ($\geq$ 52 generations). However, given the small number of loci

320 (2 - 6) and scaling of allelic effects, this represents a scenario with highly non-redundant genetics.

321 By contrast, Kondrashov and Yampolsky (1996) explored the maintenance of variation under

322 temporal heterogeneity with high genetic redundancy and found that a considerable increase in

323 variance (~3 orders of magnitude) was observed when the amplitude of the fluctuations of the

324 optimum exceeded the width of the fitness function (amplitude, $d > \sqrt{[S^2 + V_E]}$). While the

325 assumptions they made about allele effect size and number of loci meant that the local optimum

326 never exceeded the maximum/minimum possible phenotypes, the large amplitude implied by the

327 above inequality results in unnaturally large differences in fitness for a given phenotype over

328 time. For example, an individual with a phenotype equal to $+d$ would suffer a fitness cost of 86%

329 when the optimum = $-d$, when $S = d$ and $V_E = 0$. Similarly, for the standard set of parameters used

330 in their simulations where substantial variance was maintained, the fitness cost for the same

331 difference in phenotype exceeded 99%. By comparison, the fitness cost for the same difference in

332 phenotype in our simulations was 63% (under strongest selection, $V_S = 2$; this fitness cost is

333 reduced to 18% under weaker selection, $V_S = 10$). Common garden experiments typically show

334 an overall magnitude of local adaptation of ~45% (Hereford 2009), so the selection regimes used

335 by Kondrashov and Yampolsky (1996) constitute much stronger selection than normally

336 observed. Thus, while they found that temporal heterogeneity could maintain much more

337 variance than observed in our simulations, this was likely a consequence of drastic changes in

338 fitness causing the underlying alleles to cycle rapidly in frequency, with increases in V_A as the

339 alleles reached intermediate frequency. Thus, the capacity for temporal heterogeneity to maintain

340 substantial amounts of variance seems to depend upon either very extreme environmental

341 fluctuations or a narrow range of rapid fluctuations with strict assumptions on the amount of

342 genetic redundancy available. As empirical data become available for quantitative analyses of a

343 population undergoing temporal variation, this will provide a realistic standard set of parameter

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344 values to be used in theory studies, allowing for a more quantitative assessment of the likely

345 effects of temporal fluctuations, and further evaluation of the relative importance of the above

346 models.

347

348 **Spatial v. Temporal v. Combined heterogeneity**
349 Interestingly, it appears that spatial heterogeneity has a much stronger effect than temporal, both

350 in isolation and when combined. This is evidenced by the difference in magnitude of V_A

351 maintained in Sets 2 vs. 3 (pure spatial and pure temporal heterogeneity, respectively), as well as

352 the comparisons among the three scenarios of combined spatial and temporal heterogeneity (Set 4

353 A, B, C). The combination of spatial and temporal heterogeneity only marginally increased the

354 variation maintained by spatial heterogeneity alone, and only in the case of complete spatial

355 heterogeneity (Set 4B). Interestingly, among the three combined sets, V_A increased with the

356 spatial component (in general, $V_A[4C] \leq V_A[4A] << V_A[4B]$), which was robust to changes in μ

357 and V_S.

358 Thus, our results indicate that spatial heterogeneity is more important for the maintenance of

359 variation than a temporally fluctuating environment, at least for the genetic architectures and

360 assumptions about fitness used here. Additionally, from the ratio V_A/V_S (Figure 4 and S2),

361 temporal fluctuations alone fail to result in any simulation maintaining significantly more

362 variation than under homogenous conditions, indicating that it is insufficient as an additional

363 mechanism to explain the discrepancy between mutation-selection balance models and empirical

364 observations.

Does heterogeneity maintain sufficient variation to explain empirical observations?

367 Given empirical estimates of selection and heritability, a realistic amount of variation maintained

368 in a population should fall within the range V_A/V_S 0.04 ~ 0.12, which would require either an

369 unrealistically large number of loci or very high mutation rates under models of mutation-

370 selection balance, as described in the introduction. To explore whether heterogeneity could result

371 in more realistic ratios of V_A/V_S, we compared simulations run under homogeneous vs.

372 heterogeneous conditions, and examined the degree to which heterogeneity increased this ratio.

373 The shift towards this window for simulations with spatial heterogeneity suggests that this is a

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374 viable mechanism for the maintenance of variation, but is limited to populations experiencing

375 strong selection and high migration rates.

376 The results presented in Figure 4 are intended to illustrate how the maintenance of realistic levels

377 of V_A is possible under environmental heterogeneity, rather than to represent the full span of

378 parameter combinations that result in realistic behavior. Little is known about the true values for

379 many parameters involved, and changes in some values, such as the number of loci, are likely to

380 alter the quantitative results. Instead, these results illustrate that for a given set of assumptions

381 about the genetic basis of a trait, considerably more variation can be maintained by migration-

382 selection balance than mutation-selection balance. Moreover, the magnitude of this change can be

383 sufficient to explain empirical observations in some cases, indicating environmental

384 heterogeneity is a viable mechanism to consider for the maintenance of variation. However, we

385 stress that given the sensitivity of this result to the balance between selection and migration and

386 the narrowness of the region that maintains significantly more variance, it seems unlikely that

387 environmental heterogeneity will generally resolve the "paradox of variation".

Limitations

389 A major limitation to the interpretation of this study is the difficulty in comparing results to

390 established analytic models due to differences in the mutation scheme. The majority of theory

391 and analytic models assume either a single (or few with equal effect) diallelic loci, or quantitative

392 traits with a normally distributed continuum of alleles. Our simulations attempt to combine the

393 two – varying allelic effects across loci (a_i), but with a single $|a|$ per locus, and a Gamma

394 distribution of possible values a_i. We chose this approach to reflect a (potentially) more

395 biologically realistic scheme of mutation. For example, evidence suggests that the distribution of

396 allelic effects at a locus is more likely to follow a gamma rather than a normal distribution, with a

397 small number of loci of large effect and many loci of small effect (Orr, 2003). However, this

398 leads to a less straight-forward parameterization of V_m or α^2, which causes challenges when

399 attempting analytical comparisons.

400 Another limiting factor is the difficulty of obtaining measurements of migration rates in natural

401 populations, which is necessary to understand if the range where this effect of environmental

402 heterogeneity occurs is realistic. Evidence of migration maintaining quantitative genetic variation

403 in spatially heterogeneous environments was found in lodgepole pine (Yeaman & Jarvis, 2006),

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404   but genomic signatures at individual loci may be difficult to detect. Though we did not

405   specifically quantify this here, presumably there is some effect on heterozygosity, though such

406   effects could be difficult to detect in empirical data.

Implications

408   We have shown that spatial environmental heterogeneity and migration has the potential to

409   increase genetic variance substantially, while temporal heterogeneity has a much more modest

410   effect. As local adaptation is common (Hereford, 2009), this may be an important factor affecting

411   evolvability. It has been noted that conservation management lacks proper consideration of

412   evolutionary theory, implementation of which can improve overall efforts and long-term outcome

413   (Cook & Sgrò, 2017). The described effect of migration suggests that the ecology underlying the

414   maintenance of variation may be important to consider when planning conservation efforts with a

415   focus on genetics.

416   For example, a major criterion for the IUCN (International Union for Conservation of Nature)

417   Red List status is population size, however there are examples of listed populations that have

418   remained relatively stable, despite small N_e (Ex. Florida Panthers, *Puma concolor coryi*; (Benson

419   *et al.*, 2011)). The genetic consequences of population size have been emphasized due to [entirely

420   legitimate] concerns about reduced diversity, which is often used as a proxy measure for the

421   'health' of a population of concern in conservation biology. Here, we showed that a 10-fold

422   change in population size had less effect on V_A than a reduction in migration, which suggests that

423   migration may also be an important factor to consider when assessing and managing the genetic

424   health of populations of concern. Indeed, the related concepts of gene flow and connectivity have

425   been previously suggested for consideration and implementation in conservation management,

426   albeit with some contention, as too much migration can result in a reduction of variability (Weeks

427   *et al.*, 2011; Urban *et al.*, 2012; Cook & Sgrò, 2017). Long-term maintenance of evolvability may

428   depend in some cases on an intact and interconnected environment, rather than endogenous

429   generation of variation (mutation-selection), which would depend less on environment.

430   Therefore, a move towards improving connectivity between subpopulations and protection

431   against habitat fragmentation may be a pertinent consideration for the maintenance of

432   quantitative genetic variation, in addition to the well-recognized problems of reducing inbreeding

433   and mitigating demographic fluctuations.

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435   In conclusion, our results demonstrate a clear effect of migration on the maintenance of variation

436   in all four investigated scenarios, and highlight the potential for environmental heterogeneity to

437   substantially increase V_A. However, it seems unlikely that a single mechanism best explains the

438   maintenance of variation that we see in nature; rather the many concepts put forth over the past

439   decades may be viable explanations in only certain scenarios, just as has been demonstrated here

440   with environmental heterogeneity. Further investigation into potential mechanisms, particularly

441   into those scenarios under which they succeed and fail, and how biologically relevant successful

442   scenarios may be, is needed in order to get a complete picture of the fundamental process that is

443   the maintenance of variation.

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529 # Tables and Figure Captions

530 **Table 1.** Description of Parameters

Parameter	Definition	Value
N	Population size	1000, 10 000
V_S	Selection strength	2, 5, 10
μ	Mutation rate	$10^{-6}, 10^{-5}, 10^{-4}$
m	Backwards migration rate	0.00001 ~ 0.1
θ	Local (patch) optimum	
P	Periodicity; time (as the number of generations) over which temporal oscillations complete one cycle of a sinusoidal wave	4, 16, 40, 100, 1000

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532 ## Figure Captions

533 **Figure 1.** Effect of migration on the maintenance of genetic variation (V_A) in a sub-divided
534 population (N=1000) between (A) homogeneous patches, (B) spatially heterogeneous patches,
535 under combinations of different mutation rate (line colour; $\mu = \{10^{-6}, 10^{-5}, 10^{-4}\}$) and selection
536 strength (panels; $V_S = \{2, 5, 10\}$). The homogeneous environment type (broken line) represents
537 the case of mutation-selection balance.

538 **Figure 2.** Effect of migration on the maintenance of genetic variation (V_A) in a sub-divided
539 population (N=1000) between (A) temporal, (B) combined spatial and temporal, environmentally
540 heterogeneous patches under combinations of different mutation rate (line colour; $\mu = \{10^{-6}, 10^{-5},$
541 $10^{-4}\}$) and selection strength (panels; $V_S = \{2, 5, 10\}$). The homogeneous environment type
542 (broken line) represents the case of mutation-selection balance.

543 Period = 100 generations

544 **Figure 3.** Comparison of the amount of genetic variation (V_A) maintained in a population
545 simulated under scenarios with increasing degree of environmental heterogeneity, for various
546 rates of migration (*m*) and strength of selection ($V_S = \{2, 5, 10\}$; panels).

547 N=1000; $\mu = 10^{-4}$, Period = 100 generations

548 **Figure 4.** Comparison of the ratio of variance components, V_A/V_S, between simulations of
549 different pattern of environmental heterogeneity for various combinations of migration rate (*m*;
550 point colour), mutation rate ($\mu = \{10^{-6}, 10^{-5}, 10^{-4}\}$), and selection strength (point shape; $V_S = \{2,$
551 5, 10$\}$). The grey box represents the range of predicted 'typical' values expected based on
552 empirical estimates of trait heritability (h^2 0.2 ~ 0.6). Points that fall below the 1:1 line (dashed)
553 are parameter combinations under which more V_A is maintained without (A) environmental
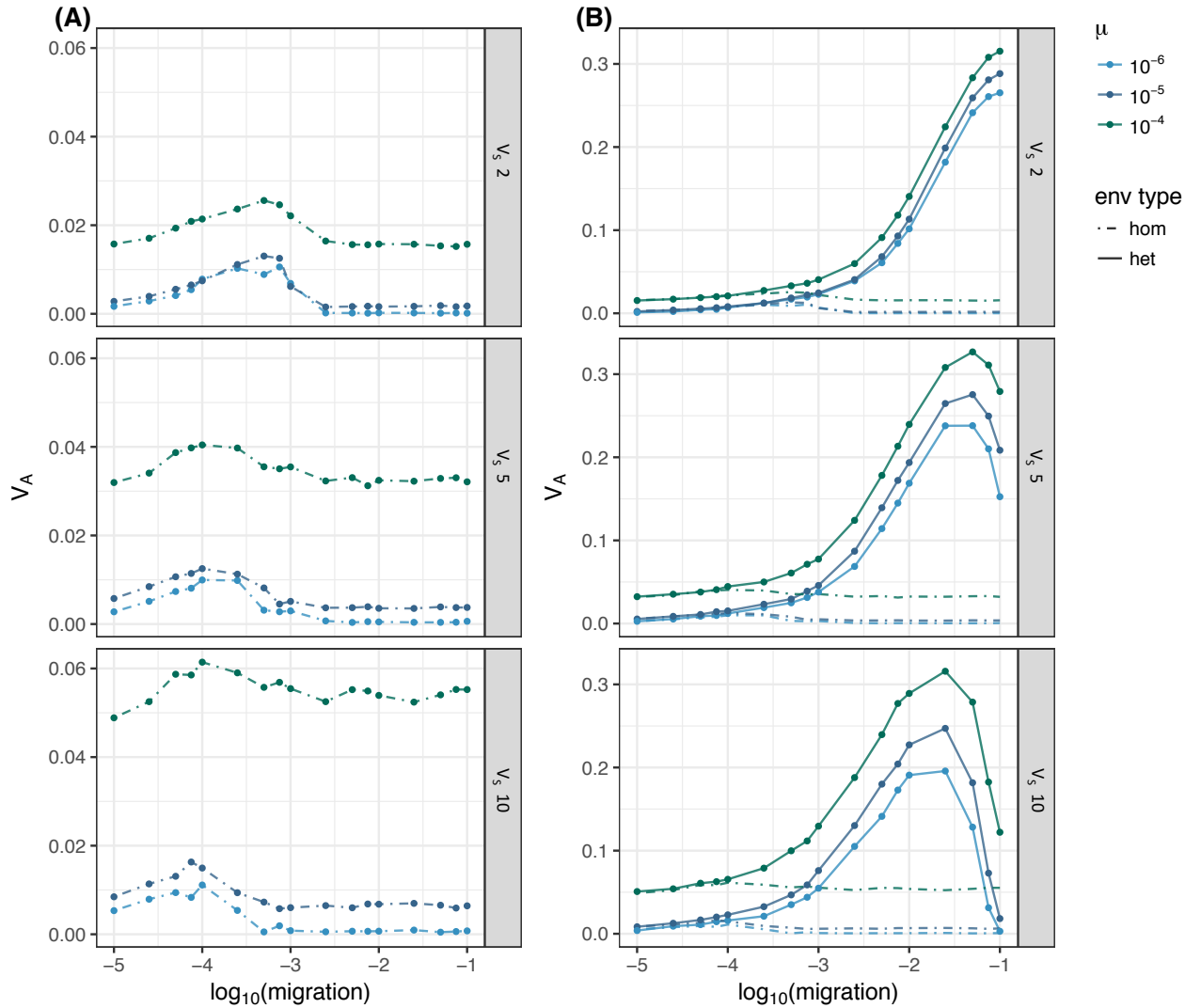554 heterogeneity, or (B) addition of temporal heterogeneity (Period = 100). N=1000

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Figure 1. Effect of migration on the maintenance of genetic variation (V_A) in a sub-divided population (N=1000) between (A) homogeneous patches, (B) spatially heterogeneous patches, under combinations of different mutation rate (line colour; μ = {10^{-6}, 10^{-5}, 10^{-4}}) and selection strength (panels; V_S = {2, 5, 10}). The homogeneous environment type (broken line) represents the case of mutation-selection balance
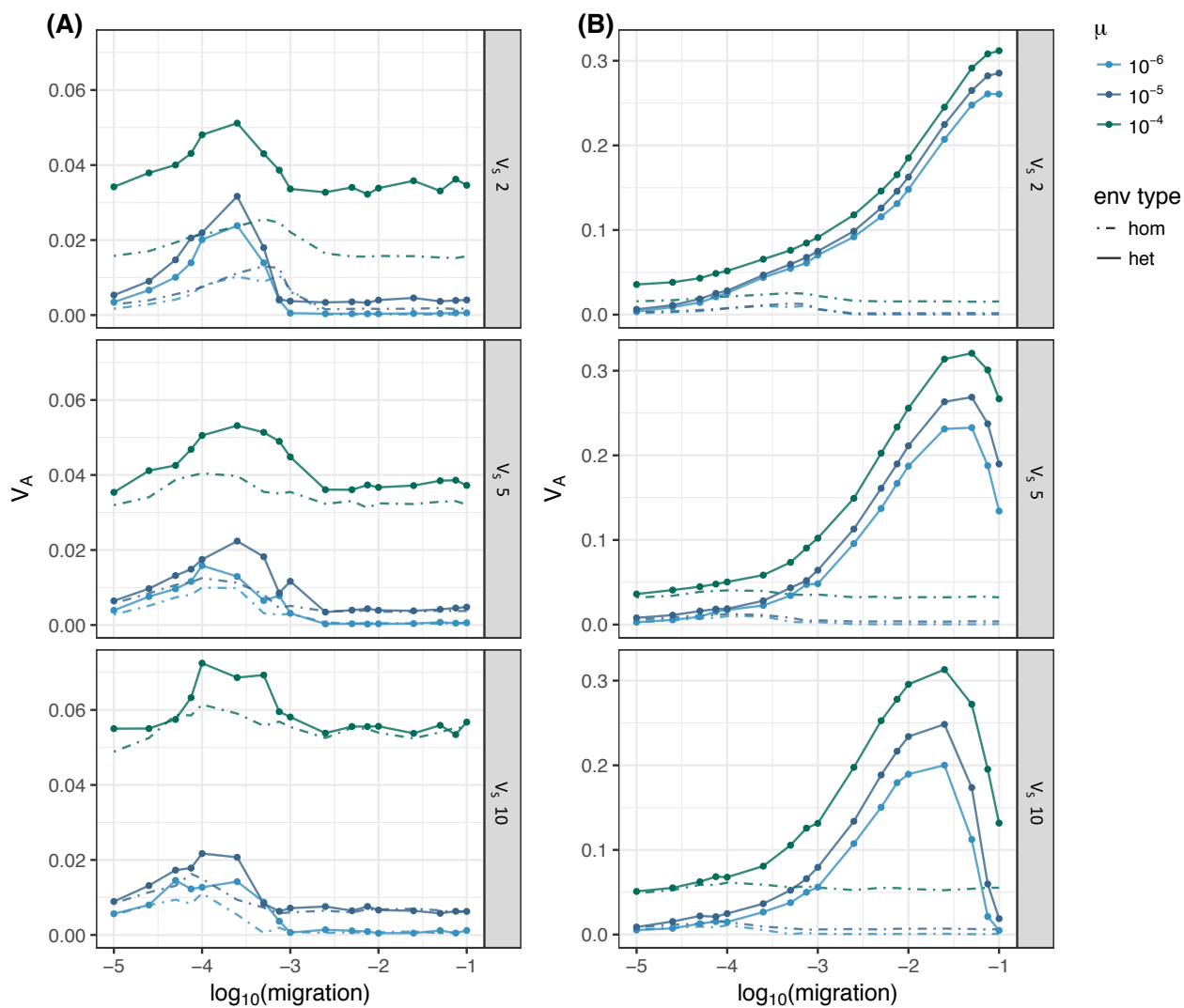
Figure 2. Effect of migration on the maintenance of genetic variation (V_A) in a sub-divided population (N=1000) between (A) temporal, (B) combined spatial and temporal, environmentally heterogeneous patches under combinations of different mutation rate (line colour; μ = {10^{-6}, 10^{-5}, 10^{-4}}) and selection strength (panels; V_S = {2, 5, 10}). The homogeneous environment type (broken line) represents the case of mutation-selection balance.
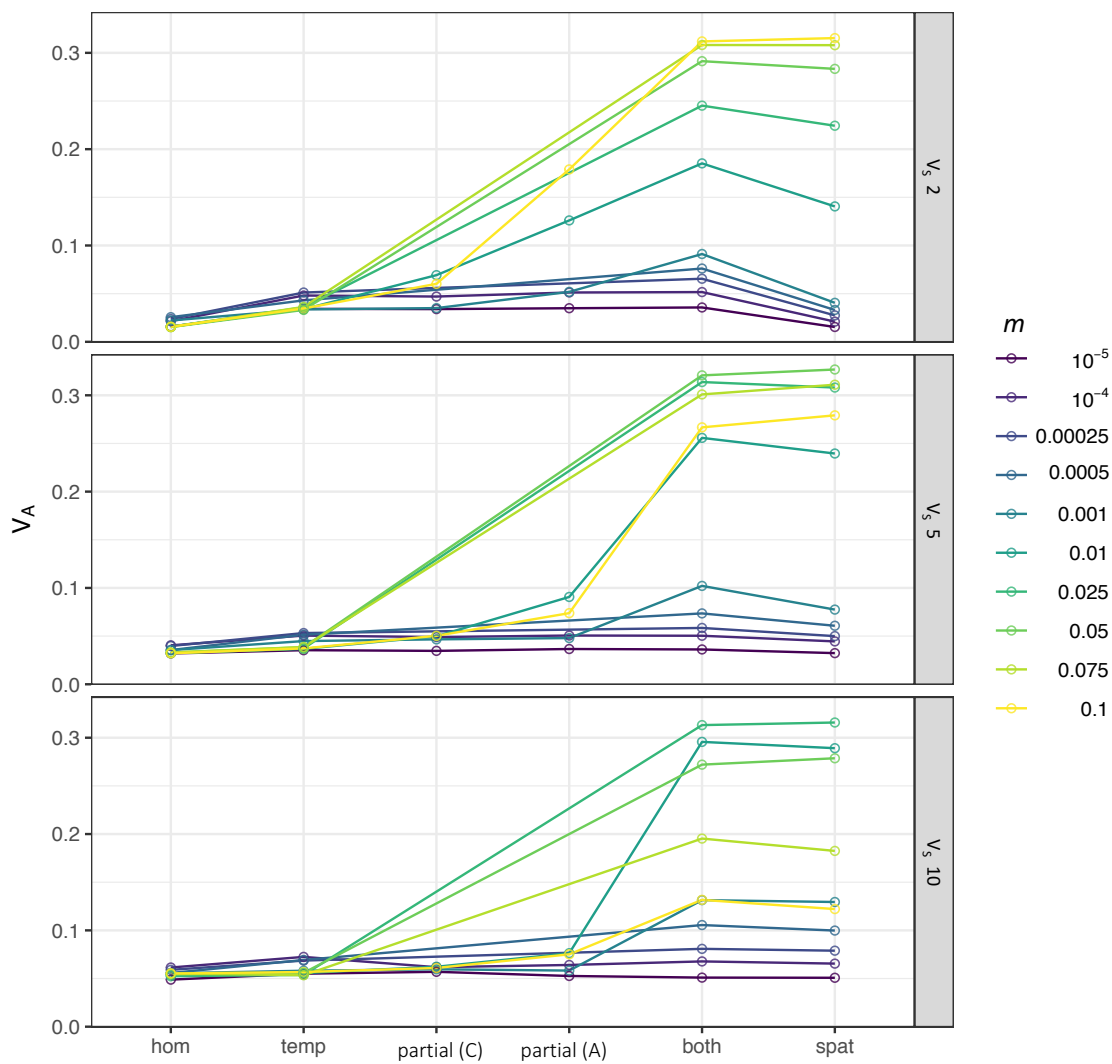Period = 100 generations

Figure 3. Comparison of the amount of genetic variation (V_A) maintained in a population simulated under scenarios with increasing degree of environmental heterogeneity, for various rates of migration (*m*) and strength of selection (V_S = {2, 5, 10}; panels).
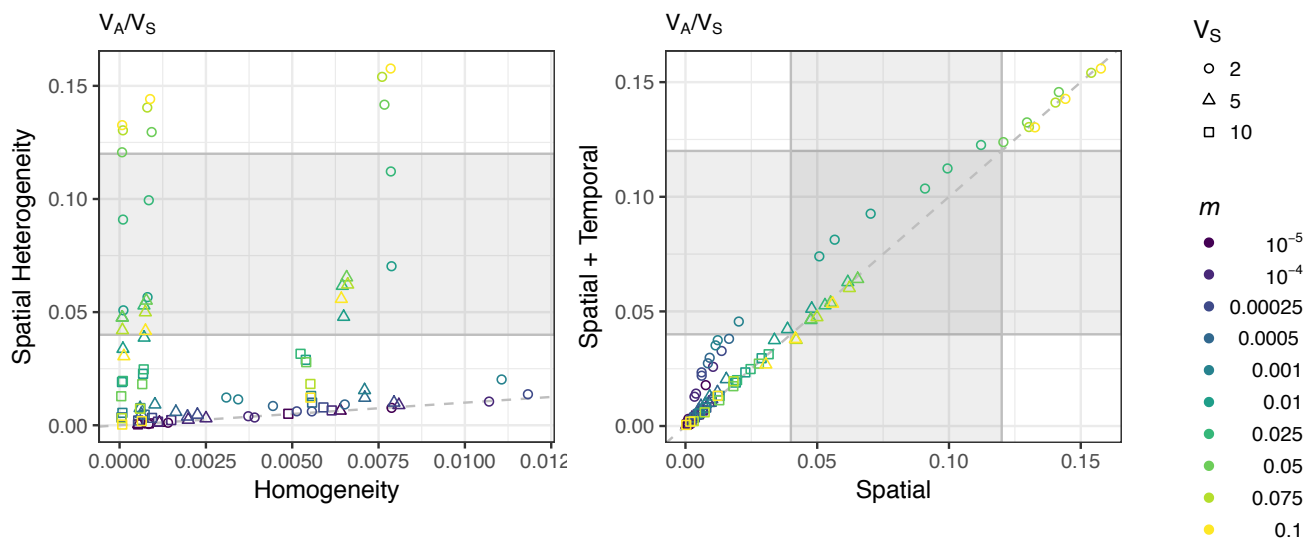N=1000; μ = 10^{-4}, Period = 100 generations

Figure 4. Comparison of the ratio of variance components, V_A/V_S, between simulations of different pattern of environmental heterogeneity for various combinations of migration rate (m; point colour), mutation rate ($\mu = \{10^{-6}, 10^{-5}, 10^{-4}\}$), and selection strength (point shape; $V_S = \{2, 5, 10\}$). The grey box represents the range of predicted 'typical' values expected based on empirical estimates of trait heritability (h^2 0.2 ~ 0.6). Points that fall below the 1:1 line (dashed) are parameter combinations under which more V_A is maintained without (A) environmental heterogeneity, or (B) addition of temporal heterogeneity (Period = 100). N=1000